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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 700603.7	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/09288	International filing date *(day/month/year)* 24 March 2003 (24.03.2003)	Priority date *(day/month/year)* 22 March 2002 (22.03.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): A01K 67/00 and US Cl.: 800/19		
Applicant ORIGEN THERAPEUTICS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of ___ sheets.

EPO - DG 1

3. This report contains indications relating to the following items:

01. 11. 2004

(107)

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22 October 2003 (22.10.2003)	17 September 2004 (17.09.2004)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Amy Nelson Telephone No. 571-272-0507

Form PCT/IPEA/409 (cover sheet)(July 1998)

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International application No.
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I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-50 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 51-52, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-10, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-8, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

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V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-20	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 1-20	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 1-20	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-20 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a culture of chicken ES cells having a transgene stably integrated into the genome, wherein the transgene is comprised of an unrearranged human immunoglobulin encoding a human immunoglobulin heavy or light chain molecule or a transgenic chicken whose genome has a stably integrated transgene comprising a human variable and joining regions.

Claims 1-20 meet the criteria set out in PCT Article 33(4), and thus meet the industrial applicability because the subject matter claimed can be made or used in industry.

---------- NEW CITATIONS ----------

F

SAYEGH et al. Avian B cell development: lessons from transgenic models. Veterinary Immunol. and Immunopath. 1999, Vol. 72. pages 31-37.

VICK et al. Transgenic birds from transformed primordial germ cells. Proc. R. Soc. Lond. 1993, Vol 251. pages 179-182.

THORAVAL et al. Germline transmission of exogenous genes in chicnes using helper-free ecotropic avian leukosis virus-based vectors. Transgenic Res. 1995, Vol. 4, pages 369-376.

LOVE et al. Trangenic birds by DNA microinjection. Bio/Technology. January 1994, Vol. 12, pages 60-63.

HARVEY et al. Expression of exogenous protein in the egg white of transgenic chickens. Nature biotech. April 2002, Vol. 19, pages 396-399.

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VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Please See Continuation Sheet

Form PCT/IPEA/409 (Box VIII) (July 1998)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

VIII. The following observations on the clarity of the claims, description, and drawings or on the questions are made:

Claims 1-20 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claims are not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because:

The art did not teach how to stably transfect chicken ES cells such that transgenesis (passing transgene through to the next generation; germline transmission of transgene) occurred. The art taught methods of transfecting chicken cells *in vivo* or *ex vivo* to obtain exogenous protein expression in a chicken, but the art did not teach using stably transfected chicken ES cells as claimed to make transgenic chickens expressing exogenous protein.

Stage XI PGCs had been isolated from chickens, transduced with retrovirus, and immediately injected into the vasculature of Stage 15 chick embryos to obtain germline transmission of a transgene (Vick et al., Proc. R. Soc. Lond., 1993, Vol. 251, pg 179-182). Plasmid DNA had been injected into the germinal disc of chick zygotes isolated before being laid to obtain germline transmission of a transgene (Love et al. Bio/Technology, 1994, Vol. 12, pg 60-63). Retroviral vectors had been injected into the subgerminal cavity of an avian embryo in a freshly laid egg to obtain germline transmission of a transgene (Thoroval et al., Transgenic Research, 1995, Vol. 4, pg 369-376). Retroviral vectors had been used to introduce a truncated antibody receptor into chickens "somatically" and express the receptor in the bursa at hatch (Sayegh et al., Dec. 15, 1999, Vol. 72, pg 31-37; pg 32, 2nd full para., lines 2-5 and 16-18; para. bridging pg 33-34). Mohammed (1998, Immunotechnology, Vol. 4, pg 115-125) taught that although using hens for the production of recombinant human antibodies (rhAb) has been discussed, it has never been demonstrated. Mohammed transfected a lymphoblastoid cell line with a retrovirus encoding a rhAb, injected the cells into a chicken and obtained expression of the rhAb in the egg yolk and sometimes the egg white (pg 116, col. 1, 2nd para.; col. 2, 1st full para.). Mohammed suggested suppressing the expression of endogenous chicken Ig but did not teach how to inactivate a gene in an avian (pg 124, col. 2, para. 2, line 9) and did not teach how to obtain a transgenic avian having an inactivated immunoglobulin gene. Since the time of filing, Ishida (2002, Cloning Stem Cells, Vol. 4, pg 91-102) suggested making chickens expressing human antibodies but did not teach how to make transgenic chickens or how to inactivate chicken genes (see abstract). Harvey (April 2002, Nature Biotech. Vol. 19, pg 396-399) taught expressing exogenous protein in chicken egg white using a plasmid encoding a protein under the control of the CMV promoter and states tissue-specific elements for adult oviducts have not been established (pg 397, col. 2, 1st full ¶) by injecting the plasmid into the subgerminal cavity of stage X embryos

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Avian ES cells were cultured for 160 days (Pain, 1996, Development, Vol. 122, pg 2339-2348). However, since the time of filing, Ivarie (Trends in Biotechnology, Jan. 2003, Vol. 21, pg 14-19) taught that because of the complex process by which a bird makes and lays eggs, transgenic procedures for birds have lagged far behind those of other organisms. Ivarie cites Pain who taught long-term culture of non-transfected, blastodermal cells that provided germline transmission; however, no transgenic birds have been made using transfected ES cells or PGCs. The biggest obstacle to overcome in making transgenic birds using transfected ES cells or PGCs is the loss of germline competence during culture of transfected ES cells and PGCs (pg 14, col. 2, 3rd full para., 1st sentence; pg 17, col. 1, 2nd full para., last two sentences; pg 17, sentence bridging col. 1-2; pg 17, col. 2, last sentence).

Thus, the state of the art at the time of filing was that stably transfected avian ES cells had not been "sustained" in culture such that a germline chimeric chicken was produced.

The disclosure does not overcome the unpredictability in the art so that the ordinary artisan could culture transfected avian ES cells and select cells having the desired knockout and obtain germline chimeras having the transgene or an inactivated immunoglobulin gene. The disclosure provides no other means of isolating ES cells, transfecting the cells or culturing the transfected cells such that the desired cells could be selected. Without such guidance, it would require the ordinary artisan undue experimentation to obtain a sustained culture or a transgenic avian having the transgene as claimed.

Claims 1-20 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims are indefinite for the following reason(s):
Claim 1 is unclear because the phrase "wherein the embryonic stem cell progeny..." does not describe a function of the culture of ES cells claimed. The phrase is also unclear because requires making a chimeric chicken; it is unclear if the sustained culture must be capable of making a chimeric chicken or if the claim should actually be a method of using the sustained culture.
The phrase "substantially" in claim 1 is indefinite because the metes and bounds of the term have not been defined in the disclosure or the art at the time of filing.
Use of the term "locus" to describe a nucleic acid sequence as in claim 1 is improper because a "locus" is a position, not a nucleic acid sequence.
Use of "immunoglobulin" twice in the last line of claims 1 and 10 is redundant.
Use of "whose genome comprises" and "integrated into the genome" in claim 10 is redundant.
The phrase "wherein a population of B lymphocytes of the chicken are a human immunoglobulin locus" in claim 10 does not make sense.
Use of the term "locus" to describe a nucleic acid sequence as in claim 10 is improper because a "locus" is a position, not a nucleic acid sequence.